Any further consideration of these facts or endeavors to interpret them would be, with the evidence at hand, idle conjecture.

CONCLUSIONS. The retention of nitrogen is one of the common phenomena associated with a large percentage of the cases of nephritis observed in hospitals. Whether this retention characterizes also, in lesser degree and periodically, earlier stages of the disease is not at present clear; but this is generally assumed to be true and is held accountable for some symptoms, whether correctly one may not assert. At those periods of nephritis when patients are forced to seek hospital aid the retention of nitrogen outside of convalescence appears to precede and lead up to either frank uremic manifestations or to the graver complications of renal disease. Furthermore, a careful study of a large number of cases discloses many where the metabolic disturbances seems confined to the protein economy, that is to say, the notable failure in elimination is in respect to nitrogen and this retained nitrogen is found not only in the blood but also in the tissues.

With some of these cases water metabolism is either normal or approximately normal and the total nitrogen elimination then appears to depend directly on the volume of water that passes through the kidneys. This is simply another way of stating an accepted fact: that the diseased kidney can not excrete a concentrated urine, *i. e.*, the power of concentration is impaired. If under these conditions the nitrogen of the diet be reduced to about half the normal and the fluid ingested be increased there results first a sweeping out of retained nitrogen and later normal approximations toward equilibrium. Reduction of nitrogen intake alone does not suffice, nor does the ingestion of large amounts of water if the diet nitrogen be not curtailed.

From a practical point of view this principle would seem to have a therapeutic application, although perhaps of narrow scope.

THE DIFFERENTIATION OF NEPHROPATHIES, CARDIOPATHIES, AND ALLIED CONDITIONS.

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THE diagnosis of renal insufficiency at present rests chiefly on the establishment of a diminished rate of elimination of certain substances normal or foreign to the usual body metabolism. It is improbable that any single, simple test will ever completely supplant a quantitative study of the water, chloride, and nitrogen balance, especially when this is supplemented by a quantitative test of the rate of elimination under conditions of stress, *e. g.*, 10 grams of sodium chloride, 3 liters of water, or 20 grams of urea added to the diet. To conduct such a metabolism study successfully requires several weeks and necessitates working with a constant or analyzed diet, besides careful separation, collection, preservation, and analysis of the twenty-four-hour urine during the period of study. It imposes, therefore, on the patient, personnel, and analyst conditions which are difficult to realize at present, either in hospital work or in private practice, even in isolated cases, and which are almost excluded as a routine procedure on a large material. It is highly desirable to have some alternative procedure which is more rapid and convenient with as little sacrifice as possible to thoroughness, accuracy, and reliability.

It is well known that the delayed elimination of certain substances in the usual forms of nephritis results eventually in the retention of these substances in the body. At present there is a lack of definite information concerning the quantitative distribution of the retained substances throughout the body fluids and tissues. It is known, however, that an increased concentration of certain substances in the blood serum occurs in many cases of nephritis. Furthermore, the blood serum is the most accessible material to study for evidence of changes in concentration, which would result from retention of sufficient quantities of the substances in question.

Through the work of Widal and his collaborators, of H. Strauss, and of P. v. Monakow, the existence of two definite forms of nephritic retention has been established. In one form water and salt are retained, while in the other there is retention of nitrogenous substances. In some cases both forms of retention occur together. While this information has been derived chiefly from metabolism studies, it would seem logical to suppose that a sufficiently prolonged retention would be followed by characteristic changes in the blood serum. The detection of these changes in the serum would depend largely on a fortunate selection of methods. Chemical methods alone would not always yield the information desired. A determination of the concentration of sodium chloride, for example, would reveal little or nothing if both water and salt were retained in corresponding amounts. Nevertheless, the resulting dilution of the serum with aqueous salt solution could be detected by physical methods. H. Strauss[1] made use of the refractometer for this purpose, and thereby called attention to the hydremic state of the blood serum, as estimated by the low refractive index, in cases of nephritis with edema.

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[1] Ztschr. f. klin. Med., 1906, lx, 501.

Other physical methods may be used to detect different changes in nephritic blood serum. The freezing-point, for example, may be taken as a measure of the concentration of relatively simple molecules, irrespective of their chemical nature. Although the freezing-point method has been more or less abandoned of late, previous reliable work has shown that there is an increased depression of the freezing-point of the blood serum in most cases of uremia. Determinations of the specific gravity have also been used to detect changes in the composition of blood serum, and hydremic sera have been recognized previously by this method.

The numerical values of the freezing-point, refractive index, and specific gravity of normal human serum are practically constants. In the pathological sera the freezing-point, refractive index, and specific gravity not only deviate from the normal, but may also vary independently of one another. These independent variations represent changes in the concentration of entirely different groups of substances. Consequently, the systematic use of these methods would seem especially applicable to the problem of nephritic retention, and should yield valuable results in the diagnosis of cardiopathies and nephropathies. This is in fact the case, and it has been possible with these methods to establish characteristic serum pictures for (1) chronic nephritis with edema, (2) chronic nephritis with uremia, and (3) chronic nephritis with both edema and uremia. Furthermore, chronic nephritis with edema may be differentiated from cardiac decompensation with edema by analysis of the serum. Finally, it is possible to recognize a group of cases which cannot be classified either as primary cardiopathy or nephropathy. These cases show persistent hypertension and an extremely concentrated serum.[2] In the absence of more detailed knowledge they may be designated provisionally as cases of primary arteriosclerotic hypertension.

In the present study the determination of the freezing-point, refractive index, and specific gravity have been supplemented by determination of the protein content and dry residue of the serum. While these supplementary determinations do not add materially to the results, they furnish a striking demonstration of the relatively large variations which are possible in the solid constituents of the blood serum in different diseases.

METHODS. The *freezing-point* was determined with the Beckmann apparatus. The customary precautions as to supercooling and inoculation were always observed. The determinations were made in duplicate, often in triplicate, and are accurate to 0.002° C. The freezing-point is designated as F. P. The freezing-point of blood serum is always below 0° C., and the numerical values are consequently minus quantities. An increased freezing-point in the text refers to one farther below zero, or with a greater absolute value, than that of normal serum.

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[2] W. H. Veil, Deutsch. Arch. f. klin. Med., 1913, cxii, 504; and 1914, cxiii, 226.

The *refractive index* was determined with the Zeiss immersion refractometer. The expression $\Delta N_d \times 10^3$ represents the difference between the refractive indices of serum and water at the same temperature multiplied by 1000. This makes the numerical results more striking to the eye without affecting their validity in any way.

The *specific gravity* was determined with an Ostwald pycnometer. The figures given are corrected for temperature and bouyancy of air. The specific gravity is designated as sp. gr. in the tables.

Group.	Case.	Freezing-point.	$\Delta N_d \times 10^3$	Specific gravity.	Dry residue.	Protein content.
I. Normals:	1 F	0.55	16.8	1.027	9.5	7.9
	2 B	0.56	17.0	1.026	....	7.7
	3 R	0.59	17.8	1.026	9.9	8.5
	4 E	0.57	17.9	1.027	....	...
	5 F	0.57	18.0	1.027	10.0	8.2
II. Cardiac Decompensation with Edema:	1 H	0.55	19.2	1.030	10.8	9.2
	2 L	0.58	17.3	1.026	9.7	8.0
	3 C	0.56	17.0	1.025	9.5	7.8
	4 H	0.56	16.4	1.024	9.1	7.4
	5 Z	0.53	16.0	1.024	9.1	7.4
	6 H	0.54	16.0	1.024	9.0	7.5
III. Chronic Nephritis with Edema:	1 H	0.59	11.0	1.015	6.3	4.3
	2 H	0.53	11.3	1.016	6.6	5.0
	3 F	0.53	11.5	1.016	6.9	5.1
	4 T	0.55	12.6	1.017	7.1	5.6
	5 K	0.57	12.8	1.020	7.2	6.1
	6 F	0.56	12.8	1.021	....	5.7
	7 D	0.54	12.9	1.020	7.3	...
	8 R	0.55	12.9	1.020	7.2	5.6
	9 G	0.56	13.0	1.019	7.6	5.7
	10 V	0.59	13.2	1.017	7.5	...
	11 P	0.56	13.5	1.019	8.8	5.7
	12 R	0.54	13.5	1.018	7.7	6.0
	13 M	0.55	14.2	1.021	8.0	6.2
	14 R	0.55	14.2	1.022	8.4	6.6
	15 G	0.56	14.3	1.023	8.0	6.3
	16 T	0.55	14.5	1.023	8.1	6.7
Sept. 28	17 G	0.57	13.1	1.022	7.3	5.8
Oct. 7	17 G	0.55	14.3	1.022	8.1	6.6
July 27	18 K	0.55	13.8	1.020	8.1	6.3
Oct. 7	18 K	0.56	14.8	1.022	....	6.7
IV. Chronic Nephritis with Uremia:	1 V	0.76	18.9	1.030	10.8	8.3
	2 P	0.68	18.9	1.030	10.7	8.4
	3 C	0.67	18.3	1.027	....	...
	4 L	0.66	18.2	1.030	11.4	9.0
	5 K	0.62	17.1	1.028	....	...
	60'S	0.61	16.5	1.027	11.1	7.8
V. Chronic Nephritis with Edema and Uremia:	1 G	0.61	15.4	1.025	8.5	7.8
	2 P	0.63	14.4	1.022	8.2	5.9
	3 C	0.62	13.3	1.022	7.4	5.3
VI. Arteriosclerosis with Hypertension:	1 G	0.59	20.8	1.033	12.2	9.8
	2 H	0.56	20.7	1.031	11.4	9.4
	3 W	0.56	19.7	1.030	11.6	9.3

The *protein content* was determined gravimetrically after precipitation by alcohol. The *dry residue* was determined in the customary manner. The results of the determinations of the protein content and dry residue are expressed as percentage weight in volume.

Ten to 15 c.c. of serum are sufficient for single determination of the freezing-point, refractive index, specific gravity, protein content, and dry residue.

RESULTS. The results are given in the table on the opposite page. The cases are arranged in groups according to the clinical manifestations. The symptoms and serum pictures of each group will be discussed in detail.

GROUP I. *Normals.* Practising physicians and assistants in the hospital who were in good physical condition served as sources of normal serum.

Serum findings.	Freezing-point.	$\Delta N_d \times 10^3$	Specific gravity.	Dry residue.	Protein content.
Average	0.57	17.5	1.027	9.8	8.1

The individual variations from the average are very small, less than 4 per cent. in the freezing-point and refractive index, and less than 0.1 per cent. in the specific gravity. The average figures for the normals serve as a basis for comparison with the figures in the pathological groups.

GROUP II. *Cardiac Decompensation with Edema. Clinical Symptoms.* These cases all presented evidence of cardiovalvular disease with decompensation, many with a previous rheumatic history. All had hypertrophied *hearts,* five showing the characteristic enlargement of mitral disease, greatly displaced right heart and conus, and the sixth, mitral and aortic disease and a pericardial effusion which was confirmed by exploration. The *edema* varied from slight puffiness of legs to general edema of the dependent subcutaneous tissues, with fluid in the pleural and peritoneal cavities. The *urine* voided varied in volume from 600 c.c. to 2700 c.c.; average specific gravity, 1.016; all contained albumin in various amounts, and casts were found in 4 cases. The *eye-grounds* were normal in all of them. Five recovered sufficiently to leave the hospital and one died, and the diagnosis of mitral disease was confirmed at autopsy.

Serum findings.	Freezing-point.	$\Delta N_d \times 10^3$	Specific gravity.	Dry residue.	Protein content.
Average Group II	0.55	17.0	1.026	9.5	7.9
Average normal	0.57	17.5	1.027	9.8	8.1

The serum is practically normal. The individual variations are somewhat greater than in the normals, and the extremes in this group surpass the extremes in the group of normals. Yet these variations are insignificant. The general average of the group corresponds closely to the normal average, but is slightly lower throughout.

GROUP III. *Chronic Nephritis with Edema. Clinical Symptoms.* All presented hypertrophy and dilatation of the *heart* to varying degrees. Systolic murmurs were noted in half the cases. The average blood-pressure was 130, with a maximum of 170 and a minimum of 110. The volume of *urine* varied from 600 c.c. to 3025 c.c.; average specific gravity, 1.019; they all contained albumin and casts; phthalein determinations were made in 4 cases:

1 H	First appearance noted in fifty-two minutes.
5 K	15 per cent. in first hour, 10 per cent. in second hour.
15 G	10 per cent. in first hour, 11 per cent. in second hour.
17 G	58 per cent. in first hour, 15 per cent. in second hour.

Edema was present in all cases, varying from pitting of the lower extremities to general subcutaneous edema and fluid in the serous cavities. Five cases showed varying degrees of neuroretinitis. No case presented any mental symptoms.

Serum findings.	Freezing-point.	Δ Na $\times 10^2$	Specific gravity.	Dry residue.	Protein content.
Average group III	0.56	13.2	1.020	7.6	5.9
Average normal	0.57	17.5	1.027	9.8	8.1

The serum in this group presents the characteristic picture of hydremia. With the exception of the freezing-point, all of the figures are much lower than normal. The serum is diluted. The normal values of the freezing-point show that the dilution is not due to water alone and that sufficient salt has also been retained to maintain the normal osmotic pressure.

GROUP IV. *Chronic Nephritis with Uremia. Clinical Symptoms.* The cases all presented very moderate degrees of cardiac hypertrophy. Systolic murmurs were noted in but 2 of the 6 cases. The average blood-pressure was 160, with a maximum of 190 and a minimum of 100. The urinary volume varied from 750 c.c. to 1650 c.c.; average specific gravity, 1.015; albumin was present in large amounts, and many casts were present; phthalein determinations were made in 5 cases:

2 P	Trace at the end of two hours.
3 C	None at the end of two hours.
4 L	None at the end of two hours.
5 K	16 per cent. in first hour, 14 per cent. in second hour.
60'S	16 per cent. in first hour, 3 per cent. in second hour.

Two of the cases presented very slight pitting of the skin over the tibiæ, but no fluid was present in the serous cavities. The *eyegrounds* were examined in 5 cases; 3 C and 4 L showed extreme neuroretinitis; in 2 P the retina was obscured by capacity of the media; in 1 V the left eye was normal and the fundus of the right eye could not be seen; and 60'S was reported normal. Three of the 6 cases had *convulsions,* and all had *mental symptoms,* varying from restlessness and anxiety to active delirium finally resulting in coma and death.

Serum findings.	Freezing-point.	Δ Na $\times 10^3$	Specific gravity.	Dry residue.	Protein content.
Average group IV	0.67	18.0	1.029	11.0	8.4
Average normal.	0.57	17.5	1.027	9.8	8.1

The serum of this group is characterized by a marked increase in the freezing-point and a slight increase in the other figures. This represents a concentrated serum with a relatively large increase in the concentration of the substances which affect the freezing-point.

GROUP V. *Chronic Nephritis with Uremia and Edema. Clinical Symptoms.* This group varies little from the last, except in the presence of edema of the extremities and the serous sacs. There was enlargement of the *heart* in all; dry pericarditis was noted in one of the cases. The average blood-pressure was 170, with a maximum of 200 and a minimum of 118. The urinary volume varies from 600 c.c. to 2200 c.c.; average specific gravity, 1.020; large amounts of albumin and many casts were present; phthalein determinations were made in 2 cases:

1 G	Trace recovered in two hours.
3 C	None recovered in two hours.

The *eye-grounds* in one case showed marked neuroretinitis (old and new); one was normal, and one case was not examined. All presented *mental symptoms* and had *convulsions.* One died, one became improved, and one well enough to discharge from the hospital.

Serum findings.	Freezing-point.	Δ Na $\times 10^3$	Specific gravity.	Dry residue.	Protein content.
Average group V	0.62	14.4	1.023	8.0	6.3
Average normal	0.57	17.5	1.027	9.8	8.1

The serum of this group presents a combination of the essential features of Groups III and IV. The freezing-point is increased and all other figures are lower than normal. This constitutes the paradox of a dilute serum with an abnormal increase in the concentration of the substances which affect the freezing-point.

The occurrence of this mixed form characterized by the coexistence of hydremia and an increased freezing-point is in thorough accordance with the results of metabolism studies on nephritics with impaired elimination of both salt (and water) and of nitrogen. Occasionally one symptom may dominate the picture to the exclusion of the others. In one of our cases not given in the table the clinical symptoms and serum findings on admission indicated an advanced chronic nephritis with edema (Group II). As his condition progressed his edema gradually subsided until he became anhydropic, simultaneous with the development of uremic symptoms which terminated in coma and death. The changes in the clinical symptoms were accompanied by corresponding changes in the serum findings:

	Date.	Freezing-point.	$\Delta N_D \times 10^3$	Specific gravity.
Flan.	Oct. 6	0.53	14.1	1.024
	Oct. 28	0.61	16.6	1.027
	Nov. 1	0.67	18.4	1.030

GROUP VI. *Arteriosclerosis with Hypertension. Clinical Symptoms.* These cases all presented the same picture of high blood-pressure with cardiac hypertrophy and dilatation, loud aortic second sound, and no murmurs. The palpable vessels were all noted as thickened to varying degrees. The systolic blood-pressures were 190, 220, and 215. The volume of *urine* was good in all cases; average specific gravity, 1.020; small amounts of albumin were present, but no casts were noted; phthalein determinations were made on all:

1 G 27 per cent. in first hour, 24 per cent. in second hour.
2 H 30 per cent. in first hour, 21 per cent. in second hour.
3 W 60 per cent. in first hour, 19 per cent. in second hour.

In all cases large, tender livers were noted. There was slight edema over tibiæ in two cases, none in the third, and the serous cavities were free of fluid. The eye-grounds of two cases were examined; one was normal and the other showed moderate neuritis with tortuous vessels.

Serum findings.	Freezing-point.	$\Delta N_D \times 10^3$	Specific gravity.	Dry residue.	Protein content.
Average group VI	0.57	20.4	1.031	11.7	9.5
Average normal	0.57	17.5	1.027	9.8	8.1

This group is characterized by a marked increase in the concentration of protein in the serum. The freezing-point is normal, but all other figures are extremely high, chiefly on account of the increased concentration of serum protein.

CONCLUSIONS. The foregoing results demonstrate the practical value of this system of analysis in differentiating the cardiopathies from the nephropathies and in classifying the nephropathies. The diagnostic results thus obtained should correspond closely to the results obtained by a study of the metabolism balance. Determination of the freezing-point, refractive index, and specific gravity of blood serum is a simple procedure and requires at most two hours, while a study of the metabolism balance covering the same ground would take at least a week. Analysis of serum by these methods possesses other advantages over the metabolism method. Retention of nitrogen or of water and salt is common to a variety of conditions, and is not necessarily indicative of nephritis. Serum analysis enables one to differentiate the cases in which retention is the result of defective renal elimination from those in which retention is due to other causes.

On the other hand there are limitations to the serum work. It is obvious that the retention of any substance must attain a certain threshold figure with respect to time and quantity before any changes could be detected in the serum by these methods. It is conceivable that a slight retention could be detected by the metabolism method before definite changes occurred in the serum. The metabolism method and serum analysis should be used to supplement each other until sufficient comparative data have been obtained.

It should also be borne in mind that the serum findings merely give a picture of the state of the serum at the time of examination. In pathological cases this picture may change from time to time with the progression or regression of the correlated symptoms. A uremic attack may clear up after several weeks either spontaneously or as a result of bleeding and restriction of protein in the diet, and the freezing-point may then return to normal. Similarly an hydremic serum may gradually change to normal during the disappearance of nephritic edema.

Serum analysis as well as the metabolism method also furnishes valuable indications as to the course of dietetic *therapy* to be followed in the different forms of nephropathies. In the uremic type a restriction of protein to the minimum necessary for maintenance is clearly indicated; at the same time the general nutrition should be kept up by increasing the fat and carbohydrate in the diet. In the hydropic form of nephropathy restriction of salt is indicated. Bleeding is beneficial in either uremic or hydropic cases. The restriction of salt or protein in the diet relieves the kidney of unnecessary work and rests the damaged function. No one would expect such treatment to remove scar tissue from the kidney or restore *destroyed structures. It may be possible, however, to prevent* a progression of the destruction of renal substance and to restore the function of partially damaged structures. At present it is impossible to foresee the beneficial results which may be derived from the dietetic treatment of early cases of chronic nephritis. It is *not unreasonable to suppose that similar results would be obtained* as in the rational dietetic treatment of diabetes.